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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB
JUDGE MARILYN L. HUFF

DECLARATION OF DR. JOSEPH O. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: May 29, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, Joseph O. Falkinham, III, hereby declare as follows:

1. I have personal knowledge of the facts set forth below, and, if called as a witness in this action, I could and would testify competently to the truth thereof.

2. As disclosed in my *Curriculum* Vitae attached hereto as Exhibit 1, I received an A.B. (Bacteriology, 1964) and a Ph.D.(Microbiology, 1969) from the University of California, Berkeley. I served in the United States Air Force Biomedical Sciences Corps directing hospital clinical laboratories from 1969 to 1972 and then accepted appointment as Fellow in Microbiology (postdoctoral fellowship) in the University of Alabama Medical Center (1972-1974). In 1974, I joined the faculty of Virginia Polytechnic Institute and State University. I have been a professor at Virginia Polytechnic Institute and State University for 26 years where, in addition to my teaching duties, I have been engaged extensively in molecular biological research. My research has focused on gene transmission mechanisms in the bacterium *Escherichia coli* (1964-1980) and on the epidemiology, ecology, physiology, and genetics of *Mycobacterium avium* (1975-present). I have published numerous research articles and book chapters, as well as directed numerous graduate student theses and dissertations in this general field.

3. Nucleic acid target capture and amplification are related to my fields of study, and I am familiar with both the non-specific methods of amplification disclosed by U.S. Patent No. 5,750,338 ("the '338 patent") and specific amplification techniques such Gen-Probe's Transcription-Mediated Amplification (TMA) system.

4. I have been retained as an expert witness in this lawsuit. I have reviewed the specification and claims of the '338 patent (Exhibit 8[1]).

SUMMARY OF OPINION

5. It is my opinion that, as of December 21, 1987, a person of ordinary skill in the art would have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying any nucleic acid sequence present in a sample by use of the non-specific amplification methods described in the '338 specification. Reading the specification, a person of ordinary skill

[1] Unless otherwise specified, all references to Exhibits shall refer to the corresponding exhibit attached to the Notice of Lodgment of Exhibits filed concurrently herewith.

in the art would *not* have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying by use of sequence-specific amplification methods incorporating specific primers, specific promoters, and/or specific enzymes.

BACKGROUND

6. Several naturally occurring enzymes create copies of nucleic acids in the cells of living organisms (i.e., "*in vivo*") in a process generally called "replication." These replication enzymes include DNA polymerases, RNA polymerases, and transcriptases. Each of these replication enzymes works by binding to a nucleic acid and producing a complementary copy of its sequence. Some of these enzymes (*e.g.*, DNA polymerases) require primers to initiate replication.

7. Each replication enzyme is named for the reaction it catalyzes. For example, a DNA polymerase catalyzes a reaction that produces a DNA polymer strand, while an RNA polymerase catalyzes a reaction that produces an RNA polymer strand.

8. Procedures that amplify DNA in a laboratory are generally performed using replication enzymes and primers, which are short pieces of DNA that bind to a portion of a nucleic acid adjacent to the sequence to be amplified. Amplification takes place when the replication enzymes are able to work in conjunction with the primers to make copies of a nucleic acid sequence.

9. The primer is used to specify the portion of the nucleic acid that will be copied. Primers bind to DNA if there are a sufficient number of complementary base pair matches. The polymerase enzyme then uses the primer as the starting point for its copying action. Generally, in laboratory amplification two primers are used to produce a copy of the sequence that occurs *between* the two points where the primers bind to the target nucleic acid.

10. Like the primers used in the amplification process, the enzymes as well can be specific or non-specific. Specific replication enzymes will only bind to a nucleic acid when the enzyme recognizes a specific sequence of nucleotide bases. However, many of those same enzymes can and have been modified by scientists, or used in particular reaction conditions (e.g., lower than normal salt concentrations), to remove this specific recognition aspect and make them

non-specific so that they can bind to and replicate a variety of different sequences.

11. Primers used in *specific* amplification procedures are selected to bind to a specific, unique sequence in a particular organism's DNA, and no other organism's DNA. Such primers are referred to as "specific" or "sequence-specific" primers. For example, the "Polymerase Chain Reaction" or "PCR" method of amplification, invented by Dr. Kary Mullis and others at Cetus Corporation in 1983, uses sequence-specific primers to amplify a specific nucleic acid sequence that is between the two primers. That specific nucleic acid sequence may be contained within a large collection of sequences, and the method thus defines a specific fragment of DNA to be selectively amplified.

12. While primers are generally designed to be specific to a particular nucleic acid target, it is also possible to produce "random" primers, which are mixtures of primers that contain hundreds and thousands of random nucleotide sequences. These primers are usually collections of short DNA fragments, averaging about 6 nucleotides in length. Short sequences that are complementary to these so-called "random hexamers" occur frequently within virtually all nucleic acids. Thus, they will bind at multiple points along any nucleic acid sequence to serve as initiation sites for replication. The target nucleic acid sequence is replicated as a set of smaller fragments, each beginning with the sequence of its initiating primer. Random hexamer primers have been commercially available since the 1970's. By using "universal" or "random" primers in an amplification process, it is possible to avoid the labor and cost that would be necessary in order to develop specific primers for each target nucleic acid. The trade-off in using random primers is that the amplification process will not be specific for the sequence of interest, and instead will amplify any nucleic acid present in the sample (including sequences that are not of interest).

13. "Specific" primers and enzymes will function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer(s) and/or recognized by the enzyme is present in the sample. By contrast, non-specific primers and enzymes will amplify *any* sequence present in the sample because some random primers will bind to the sequences in the sample and non-specific replication enzymes will catalyze the reaction without regard to the sequence.

THE MEANING OF CLAIM TERMS IN VIEW OF THE '338 PATENT'S TEACHINGS

14. The '338 patent describes combining target capture with *non-specific* amplification of the captured nucleic acid sequence. By "non-specific amplification," I mean that the primers described in the patent are not pre-selected to bind to specific nucleotide sequences as part of the amplification process. The enzymes described in the patent are also non-specific and will cause replication of any sequence. My opinion about the meaning of the term "amplifying" is based on my understanding of the state of the art at the time the application for the '338 patent was filed and the description of the invention set forth by the inventors in the '338 patent. I discuss the reasons for my opinion below.

Introduction to the Patent Specification

15. In the "Background of the Invention" section, the patent defines the term "amplify" in very broad terms that encompass many different methods of amplification, including many that were already well-known in the art. Throughout the remainder of the specification, however, the inventors teach only non-specific amplification, a subset of the methods known in 1987, because -- the inventors say -- a benefit of their invention is that it *eliminates* the need to design and prepare specific primers and/or the need to use specific enzymes. [The '338 Patent at column 30, lines 30-40.] Thus, the inventors intentionally teach the use of amplification methods that are significantly more limited than the full range of amplification methods known in the art at the time. The inventors' description of their invention narrowed the term "amplify," with respect to the invention, from the general definition initially set forth in the "Background of the Invention."

The Fundamental Teaching Of The '338 Patent

16. The '338 patent presents seven examples of the methods taught by the inventors. In the first three examples, the inventors refer only to methods of target capture, without an amplification step. In the last four examples, the inventors teach combining a target capture step with amplification methods.

17. Between the end of the target capture examples (Examples 1-3) and the first example to add an amplification step (Example 4), the inventors expressly set forth their teachings with respect to amplification methods. Referring to the target capture methods described in

Examples 1 through 3, the inventors stated:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

18. The inventors then stated *why* they had chosen to combine their target capture methods with non-specific amplification. The inventors stated that the target capture step of their method made specific amplification primers and enzymes unnecessary:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ ***non-specific*** *enzymes or primers...* ***Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.***

(*Id.* at col. 30, ll. 30-40, emphasis added.) A person skilled in the art as of December 1987 would have understood from this description that a primary benefit of this invention was that it used "standard" primers and reagents for all amplification reactions. A person skilled in the art would have understood that, by using the method of the invention, one would not need to design and test specific primers for each particular target organism and/or use other individualized reagents. When the patent says that "no specifically tailored primers are needed ... and the same standard reagents can be used, regardless of targets," one skilled in art would conclude that the invention does not encompass methods of *specific* amplification. In fact, the inventors tell one of ordinary skill in the art that there is no need for specific amplification using their method.

The Drawings and Examples Of The Patent

19. The first pages of the '338 patent provide drawings of various methods encompassed by the invention. The drawings are discussed and described in sections in the sections entitled "Brief Description of the Drawings" and "Detailed Description" ('338 Patent, Exh. 8, at cols. 9-19.) The drawings are also referred to in the "Examples" set forth in the final section of the specification, immediately preceding the claims (Columns 24-32).

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20. The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification. Figures 4, 5 and 6 depict a target capture step followed by an amplification step using only non-specific primers or enzymes. The patent text expressly states that in each of these drawings "the isolated target is *non-specifically* amplified to form a multitude of amplification products." (*Id.* at col. 15, ll. 56-58, emphasis added.)

21. In the "Examples" section of the patent, the inventors set forth seven examples to further describe their invention (*Id.* at col. 24 to 32). As discussed above, the first three examples describe target capture methods, without amplification. After Example 3, the inventors set forth the fundamental teaching of the '338 patent with respect to the use non-specific amplification (discussed in paragraphs 19 and 20 above). Then, the inventors present four examples of amplification methods combined with target capture (Examples 4 - 7). Although these four examples describe different amplification methods, all of those methods describe *non-specific* amplification. Each of these examples is consistent with the earlier teaching of the patent that sequence-specific primers and specific enzymes are not necessary.

22. The Drawings, associated text, and Examples do not describe methods that combine target capture with sequence-specific amplification methods using specific primers or enzymes. The absence of such references is consistent with the patent's core teaching that the burden of specific amplification methods can be avoided when the inventor's methods are used.

Figure 4 and Example 4

23. Figure 4 and Example 4 of the '338 patent describe only a form of non-specific amplification, namely, non-specific transcription.

24. In describing Figure 4, the patent states that the amplification reaction uses "core RNA polymerase" to produce to produce a complementary RNA. (Col. 15, ll. 59-61; see also Fig. 4, Step 3). Core RNA polymerase lacks an accessory protein (the sigma protein) that endows the core enzyme with the ability to bind to certain nucleotide sequences and initiate RNA synthesis (Example 4, column 30, lines 59-66). The core RNA polymerase, lacking sigma protein, binds anywhere on a DNA, thus producing a variety of complementary sequences (Figure 4, step 3, and Example 4 (Col. 31, lines 5-16)). Thus, core RNA polymerase amplifies non-specifically by

transcribing[2] *any* sequence with which it comes into contact. Example 4 further states that other "RNA polymerases *that lack transcriptional specificity*..." can be used in place of the particular polymerase suggested by the inventors (Col. 30, line 66 to col. 31, line 1).

25. Figure 4 and Example 4 describe only non-specific amplification. Figure 4 and Example 4 do not describe the use of sequence-specific primers or enzymes in the amplification step. The method described by the inventors in Example 4 is consistent with their earlier teaching that no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.

Figure 5 and Example 5

26. Figure 5 and Example 5 describe a form of non-specific amplification in which the isolated target DNA is non-specifically replicated and then non-specifically transcribed:

> In this example, both *non-specific* replication of target DNA and transcription of that DNA are used to amplify capture target DNA.... Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. . . .

('338 Patent, Exh. 8, at col. 31, l. 24-54, emphasis added.)

27. In Figure 5, the inventors describe a "two enzyme amplification system" that uses, first, in step 3(a), a DNA polymerase with random hexamer primers to make DNA strands, and second, in step 3(b), core RNA polymerase to form additional RNA complements of the DNA (Col. 16, ll. 10-16; Example 5, col. 31, lines 25-53). As previously set forth, core RNA polymerase amplifies *non-specifically.*

28. Further, because of the limited number of primers of the same sequence in the mixture of random hexamers, there would be little accumulation of specific sequences. The primers become part of the amplified product and are thus consumed.

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[2] "Transcription" is a process of nucleic acid synthesis in which an RNA polymerase makes a single-stranded RNA copy of a DNA strand. Transcription does not require primers. In non-specific transcription, the RNA polymerase initiates synthesis randomly at multiple points along the DNA. Specific transcription occurs when the RNA polymerase with sigma protein recognizes and binds to a specific sequence in the DNA called a "promoter." The RNA is then synthesized beginning at that point.

29. The "hexamer primers" and "random oligohexamer primers" described in Figure 5, step 3a, and Example 5 (col. 31, lines 31-32) are commercially available pieces of DNA six bases long, that are a collection of random nucleotide sequences (see col. 31, lines 32-33). The hexamer primers and DNA polymerase depicted in Figure 5, step 3a, would indiscriminately replicate any nucleic acid sequences present in the reaction mixture, which is explicitly stated in Example 5 ("*non-specific* replication of target DNA." (Col. 31, ll. 24-25, emphasis added.)) Thus, a family of different sequences would be produced as a result of the non-specific amplification. Further, because mixtures of random hexamers will vary, the products of non-specific amplification would differ from individual experiment to experiment.

30. In the second enzyme step described in Figure 5, step 3b, and in Example 5, non-specific RNA polymerase is added to non-specifically produce many RNA copies from the DNA.

31. Thus Figure 5 and Example 5 describe only non-specific amplification. The inventors described and illustrated a method that is consistent with the teaching of the patent that no specifically tailored primers are needed for each test, and that standard reagents can be used, regardless of target nucleic acid.

Figure 6 and Example 6

32. Figure 6 and Example 6 describe only non-specific amplification of a "captured" nucleic acid, using DNA polymerase and "non-specific" or "random hexamer primers" to bring about non-specific double-stranded DNA synthesis (Figure 6, Step 3a; col. 16, lines 17-23; Example 6, col. 31, lines 63-64).

33. The amplification process described in Example 6 and illustrated in Figure 6 is a cycling method similar to the cycles of synthesis used in the PCR method, but the method described in the '338 patent does not use sequence-specific primers. Instead, the method taught by the inventors in the '338 patent describes the use of a target capture step to isolate the target nucleic acid from other nucleic acids, followed by multiple cycles of DNA synthesis, each initiated by using random hexamer (e.g., non-specific) primers. There would be no accumulation of unique sequences, because of the consumption of primers during non-specific amplification.

34. Example 6 states that the amplification step described therein (and depicted in Figure 6) uses DNA polymerase and "*random* hexamer oligonucleotides to bring about *non-specific* double-stranded DNA synthesis" ('338 Patent, Exh. 8, at col. 31, ll. 63-64, emphasis added).

35. Thus Figure 6 and Example 6 describe only non-specific amplification. The method described by the inventors in Example 6 is consistent with their teaching that no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of the target sequence.

Example 7

36. In Example 7, the inventors describe another method of non-specific amplification. (There is no drawing in the patent that depicts the method of Example 7.)

37. In Example 7, the inventors describe a *non-specific* amplification method that uses an RNA polymerase, Qß replicase:

> In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase...

('338 Patent, Exh. 8, at col. 32, l. 10-19, emphasis added.)

38. Thus Example 7, like Examples 4, 5 and 6, also discloses only non-specific amplification of a captured nucleic acid. This method is also consistent with the inventors' teaching that the methods of their invention do not require specifically designed or predetermined primers and that the same reagents and replicase can be used for each test, regardless of the target.

Procedures

39. The '338 patent describes certain procedures to be used in connection with the invention (columns 19-24).

40. In the "Procedures" section, the inventors did not prescribe any procedures for designing, making, or using sequence-specific primers or enzymes, nor any procedures for combining target capture with methods of specific amplification. This omission is consistent with the teaching of the patent that specifically tailored primers are not needed for any test, and the

same standard reagents can be used.

The Understanding of A Person of Ordinary Skill in the Art at the Time of Filing

41. I understand that a term in a patent claim will be given the meaning that would have been understood, based on the description provided by the inventors in the patent, by one of ordinary skill in the art. I further understand that the meaning is determined as of the date on which the first patent application was filed for the claimed invention. I have been informed that the applicable date in this case is December 21, 1987.

42. A person of ordinary skill in the art in December 1987, reading the '338 patent specification, would understand the term "amplifying" in the claims to mean using non-specific amplification methods (such as those described and illustrated in the patent).

43. In the '339 patent, the inventors explicitly teach that the benefit of their invention is that it allows the use of non-specific amplification. The inventors apparently believed that the specificity of the target capture step of their method permitted scientists to avoid the need for specific amplification:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ ***non-specific*** *enzymes or primers...* ***Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.***

(*Id.* at col. 30, ll. 30-40, emphasis added.)

44. This express teaching of the patent is reinforced by the fact that the only amplification methods that the inventors chose to describe and illustrate with Examples and Drawings are non-specific amplification methods.

45. Further reinforcing my conclusion is the fact that PCR, the most commonly used sequence-specific amplification method at the filing date, is not included, described or referenced in the specification. Moreover, the specification does not contain a reference to any other

sequence-specific amplification method.

46. If the inventors had intended to suggest and claim the combination of target capture with sequence-specific amplification methods such as PCR, it would have been easy for them to do so. The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985. Within the scientific community, PCR was immediately recognized as a significant improvement over earlier methods of making copies of nucleic acids, and knowledge of the method was widespread.

47. Although the application leading to the '338 patent was filed two years after PCR was publicly disclosed, the patent does not describe or teach a method that combines target capture with amplification methods using specific primers, such as PCR.

48. Although the '338 inventors could have included an example in the patent that combined target capture and sequence-specific amplification (such as PCR), the inventors instead described a method to *avoid* using sequence-specific primers. That is, the inventors suggested their invention as an *alternative* to specific primer methods such as PCR.

49. In all of their drawings, descriptions, and examples included in the '338 patent, the inventors clearly taught that by adding the specificity of a target capture step, scientists could avoid the need to use specific primers and enzymes in the amplification step of a nucleic acid assay.

50. I understand that the patent statute requires that the patent set forth enough details to enable a person skilled in the art to make and use the invention, as it is claimed, without requiring more than routine experimentation. It is unclear to me how the '338 patent enables a person of ordinary skill in the art as of December 1987 to use methods that combined target capture and sequence-specific amplification techniques, when no such methods were described in the patent.

51. I also have been informed that the patent statute requires that the "written description" of the invention set forth in the specification patent must demonstrate that the inventor(s) had actually invented the invention, *as it is claimed*, when the patent application was filed. The '338 patent does not show that the inventors invented any methods that combined target

capture with sequence-specific amplification, and the patent in fact tells those skilled in the art that specific amplification is not necessary when the invention of the patent is employed. Specific amplification cannot, therefore, be a part of the invention.

SUMMARY

52. A person of ordinary skill in the art, reading the '338 patent, would understand the term "amplifying" as used in the claims to mean amplifying with the methods of non-specific amplification described in the patent. Moreover, upon reading the '338 patent, a person of ordinary skill in the art would not have understood the term "amplifying" as used in the claims to mean amplifying by using sequence-specific primers, and/or specific enzymes in methods of sequence-specific amplification.

I hereby declare under penalty of perjury under the laws of the United States of America that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. As discovery in this case is now just beginning, I reserve the right to change my opinion. This declaration was executed by me on this 26th day of April, 2001 at Blacksburg, Virginia.

Joseph O. Falkinham, III